

**Congenital Cytomegalovirus: Information for State EHDI Programs  
Considering Dried Blood Spot Screening or Testing**

**Speakers:**

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**Sheila Dollard**, Centers for Disease Control and Prevention

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**Danielle Ross:**

I will start with welcome and purpose of the call. Thank you very much for joining this call. This is an informal call to provide states with up-to-date information on using dried blood spots for screening or testing for congenital CMV. The idea came about during one of the CDC-EHDI check-in calls with Nebraska. Jeff Hoffman inquired about what other states were doing with regard to congenital CMV using dried blood spots. I thought this would be a good opportunity to have a conference call. This call is for people to get a good idea of what other states are doing and to get up-to-date information. I sent around some of Jeff's slides yesterday on the listserv. However if you didn't get them, that's no problem because Jeff will be going over that material verbally. Okay. So are there any questions about the purpose of the call? We'll move on to item number two. Mark, before you start can you please give a short introduction so people know a little bit of your background regarding dried blood spots and screening for congenital CMV?

**Mark Schleiss:**

My name is Mark Schleiss. I'm a professor of pediatrics at the University of Minnesota and Director of the Division of Pediatric Infectious Disease here at the university. I've been interested in CMV for quite a number of years working on both laboratory-based models for congenital infection, vaccine strategies to prevent infection and disease in newborns and some of the clinical epidemiology work we've been doing with the state of Minnesota. So what I will do is make just a few comments about some of the work we've been doing here in Minnesota on this question. So I'll just pause there and let Sheila make a few comments.

**Sheila Dollard:**

My name is Sheila Dollard and I'm a laboratory director focusing on developing diagnostic assays for herpes viruses. We became very interested in CMV three or four years ago and my CMV focus has been serology, assays and fine-tuning assays. Using dried blood spots for detecting congenital CMV has been my recent focus that's related to this conference call.

**Danielle Ross:**

Thanks. Okay. Mark, if you could just go ahead.

**Mark Schleiss:**

Sure. Well I'll make a few comments about some of our observations here in Minnesota and then some personal observations, I guess, on what I see as some of the big challenges in this area. I relocated to Minnesota about three years ago after having been at Cincinnati Children's Hospital for the previous 15 years. And one question that I really wanted to sort of deal with in Minneapolis and in the twin cities was the issue of dried blood spot screening for congenital CMV. I found that the state health department here in Minnesota was very collaborative in nature and very cooperative and interested in working together on this question so it was really a terrific opportunity to try to do some work in this area. There are about 70,000 babies born every year in Minnesota and we began our focus on only those infants that fail the newborn hearing screen. To ask the question whether or not there was a disproportionately high representation of congenital CMV infection in that group. Some of the challenges in that area, of course, center around issues about newborn hearing screening and its accuracy and predictive value. I think many people on this call surely recognize a lot of failed newborn hearing screens occur in a situation where in fact the baby has normal hearing and these are false positives, if you will. Which is certainly acceptable from a screening test perspective but it does muddy the water a little bit when you're throwing in the CMV question. So to begin to deal with this issue we decided initially to limit our screening just to those babies that failed the newborn screen and then to have a control group matched by zip code of infants who pass the screen. And we've been working on this project now for about two years. We've looked at somewhere in the range of a couple thousand blood spots in each group. What we have found is that there is a disproportionately high percentage of congenital cytomegalovirus infections in the blood spots of babies who failed the screen somewhere in the order of 3.5% to 4%. The background is in the range of .5% which fits well with what Jim Bale described in Iowa of about .5%. The prediction would be in the upper Midwest which is mostly Caucasian population with a lower seroprevalence of women of child-bearing age of other states one wouldn't expect to see more than about .5% congenital infection rate. Some spin off projects that we've been working on are to look at some viral pathogenesis related genes in these infants who have evidence of congenital infection. There are a number of genetic markers that various groups have postulated may be related to increased pathogenesis including variation in genes like the UL144, which is a tumor necrosis factor encoded by the virus glycoprotein B, which has a number of polymorphisms. These are some of the questions we're addressing. I think one challenge in all of this is to sort of decide who should be screened. Are we talking about a test that should be utilized for general population screening, in other words, all newborns, or should we be focusing on those babies that fail the newborn hearing screen? Now, the danger in that and I'm sure that this is something that Jeff will allude to in a few minutes, the danger with that is most infants, of course, with congenital CMV infection who are destined to have some degree of hearing loss will have normal hearing at birth. That becomes a challenge that might justify a universal screening approach.

One of the dilemmas from the universal screening approach is the fact most infants who have congenital CMV infection are in fact going to be normal, at least we think so. Most congenital infections are asymptomatic and we don't think have any long-term neurological developmental consequences. Are we creating a scenario where we're creating a vulnerable child syndrome by falsely raising alarm and concern in parents? Personally, I think that's not an ethical issue because we do this all the time with other newborn screening paradigms. Most infants who test positive for congenital hypothyroidism in Oregon don't really have hypothyroidism. I think it is

acceptable. I think it's an ethical point that warrants some discussion. There are two other big challenges as I see it. One is the sort of plethora of different kinds of PCR assays that are flowing around out there. If we're going to compare information from Minnesota with information from Nebraska with information from California, you know, in principle we would be using the same assay with the same degree of sensitivity but in fact there is a wide range of different kinds of real time PCR assays out there. Some are based on technologies, some are based on light cycler technologies. Probes for PCR and target signals for amplification vary from lab to lab. Some labs concentrate on the DNA polymerase gene which is what we're using because it is very highly conserved among different isolates. Other protocols use glycoprotein B. I think it's a question in the field that needs to be resolved. I think the other issue that merits some discussion is that indeed are all babies with congenital CMV destined to have some risk for sequelae? It certainly is plausible that babies can have congenital infection as demonstrated by the presence of virus in a urine culture and not have positive PCR signal in the blood. Now my sort of anecdotal experience, if you will, suggests to me that in fact the blood PCR appears to be very, very sensitive and I have been impressed, in fact, at the number of babies I see in my clinic with congenital CMV infection who have pretty high-grade DNA-emia sometimes for months. I think we're going to pick up the majority of cases of congenital CMV that we need to be concerned about. There are data from Shannon Ross and Karen Fowler and the group at Birmingham, Alabama, that suggests that the risk of sequelae is directly related to the magnitude of viral load in the blood. That is reassuring with respect to blood spots being sufficient to identify babies that are at risk. But be that as it may, I think it is still an open question in the field. One algorithm that we're discussing currently with the state health department here as a part of our ongoing studies is to follow up the PCR blood spot analysis with a second tier test that would involve either having the parent collect urine on filter paper at home in a diaper or have a referring pediatrician become involved and trying to confirm the diagnosis with urine, saliva or additional blood samples. There may be a role for serology in this, too, that is fraught with lots of difficulty because most antibodies are going to be transplacental and the IGM test is not particularly reliable, although Sheila may have some comments on that. I think the last point is a sort of a huge issue that probably most of the people on this call have a better understanding of than I do but it's the ethics and civil liberty issues. In Minnesota we're very fortunate all blood spots are saved in a warehouse where we can easily track them down and recall them. We have done our initial studies with blood spots in an anonymous fashion. The next step will be to include identifiers to try to track these babies but there is a small but very vocal minority of people, lay people, who are vociferously opposed to saving these blood spots and some states in fact mandate they be destroyed after a certain period of time. The availability of these for clinical research is very much a state-to-state kind of challenge and here, too, I think we suffer from a lack of uniform approaches on a state by state basis and that ultimately is sort of a political issue that we can't have a huge amount of control over, I suppose, but it is a concern.

So in summary, we've been very excited by this work and we think ultimately it will help to identify these babies so that early intervention can be offered and they can be followed carefully over time. But there are issues about the variability of assays from one lab to another. 1) The correlation of DNA-emia with congenital infection with babies who may have only evidence of virus in the urine but not the blood and 2) some of the ethical and civil liberty issues in terms of long-term follow-up. I would also again reiterate that it's a big challenge, I think, to answer whether this should really be universal screening or selective screening recognizing that most

babies with CMV who are going to have hearing loss in fact have normal hearing at birth. I guess the last point I would sort of throw out, too, it's not at all trivial and that point is who pays for this. And if we can enlist our state legislatures and partners in the political arena to recognize the value of this, then that might be a strategy to help make this a standard of care some day but state budgets being spread so thin as they are, it's a challenge in my view to figure out sort of who ultimately will have financial responsibility for covering the costs of this test. So those are sort of my thoughts and comments and I'll stop here, but hopefully this has stimulated some thoughts and some questions from those on the call.

**Danielle Ross:**

Thanks so much, Mark that was really informative. I guess we should continue maybe with a few questions and then Sheila you can take the stage. Are there any questions specifically for Mark?

**Caller:**

How stable is the viral DNA?

**Mark Schleiss:**

The blood spots are stored in a sort of -- cool humidified warehouse environment. It is basically about four degrees centigrade. They are bagged and packaged in plastic and sort of archived in boxes in batches. One question that comes up in this area is there a risk of false positives because one card is sort of sitting next to another card in the sequence. We've looked at that and not found that to be an issue but we have done some experiments where we've gone back and pulled the cards that were immediately adjacent to a positive to see if any of the DNA rubbed off, if you will. I think the stability of the DNA is not a major concern. Cytomegalovirus is a DNA virus, obviously, my sense of it is, although we haven't rigorously looked at this, the stability of the DNA over time is excellent. We've gone back to some blood spots as old as four and five years old. One of my fellows has a project in which we retrospectively recall the blood spots of all children who present to our otolaryngology clinic with unexplained deafness. We have positives that go back at least a few years. I think the stability of the nucleic acid is much more an issue with RNA viruses. It has come up with issues and HIV. My bias is that the stability of the nucleic acids will not be a problem.

**Caller:**

Thank you.

**Danielle Ross:**

Any more questions before Sheila takes the stage?

**Ellen Amore:**

This is Ellen from Rhode Island. Mark, how does the cost of the PCR compare to other newborn dried blood spot screenings? Because in my mind it seems like it's pretty high.

**Mark Schleiss:**

Well, it is. And I think this is a concern. I think that the biggest cost for us is in the procurement and extraction of the nucleic acids. I think this is an issue that will have to be addressed long

term. What we currently are doing is getting three, three millimeter punches from the cards that are then transported to us by the state health department. Those individual punches in turn have to be extracted using very sensitive techniques, obviously. We don't have a lot of blood there for one thing - a few micro liters at best. We looked at a wide variety of automated and semi-automated extraction techniques and settled upon a semi-automated extraction technique that involves an initial overnight incubation, containing buffer followed by extraction on an automated machine made by Corbet. We found there is some variability in the DNA extracting machines. It's one thing when you have five mls of blood from an adult bone marrow transplant patient. Then I think you can accept you're going to have some losses during the extraction process. Under these circumstances you can't accept that. You have to try to extract every molecule of DNA from the blood spot. That's where the cost is in my view. We're talking about a test in various labs people charge anywhere from \$70, \$80, up to \$300. So for this to be practical we have to resolve this issue.

**Ellen Amore:**

It seems like you're screening for a risk. Not even screening for an identified condition which you are with the other newborn blood spot conditions.

**Mark Schleiss:**

Well I think that's an excellent comment. And this harkens back to my earlier comments about are we creating a problem where one need not exist? Are we creating a vulnerable child syndrome, if you will? We are screening for risk - in most of these kids. On the other hand, we know that perhaps as many as 10 to 15% of these infants are going to have clinically significant sensorineural hearing loss. By identifying them in the newborn period it creates a window of opportunity for assessment, audiologic assessment and early intervention. I think that our early intervention and approaches to hearing loss in newborns are, in spite of our best efforts, still in need of improvement. I'm not an economist and I think somebody that understands how to do these sorts of equations should look at this. My view of it would be if you do a cost benefit analysis you could probably show it would be cost effective for the subset of babies who are going to have disabilities related to this. Your point is very well taken. I think that this is a big challenge in this area.

**Ellen Amore:**

Thanks.

**Nancy Greene:**

This is Nancy Greene from Columbia. That was great. I hope you can post your slides somewhere where we can download them. It was an excellent presentation. Just to address the question about cost for the DNA extraction - there's some nice work being done out of Wisconsin led by May Baker. She has a system where she doesn't do any hands on DNA extraction, DNA-PCR-based assay. She has sort of a solution one and solution two that she uses. I'm not sure exactly what is in them. It really reduces the amount of manipulation needed for the sample to get high quality DNA.

**Mark Schleiss:**

Thank you. That's good to know. I will certainly look at some of her papers or protocols.

**Nancy Greene:**

I'm not sure it's published yet. You may have to contact her.

**Danielle Ross:**

Sheila would you like to give us a summary and take the stage? Then we can continue with questions for both Sheila and Mark

**Sheila Dollard:**

I do have a few things to add to what Mark said. I agree with pretty much everything Mark said about what the major challenges and issues are. The relevant study that my lab just completed was screening of 5,000 dried blood spots from California for CMV. We used a six millimeter punch to extract PCR and before we began, I talked to Harry Hannon at the CDC. The use of dried blood spot material is competitive. I asked him if in the future CMV were added to the screening test what would be the largest possible sample we would ever hope to get. That was his answer. I know laboratories that use the entire dried blood spot. My response to that is why bother? You would never get that in a newborn screening program so our assay development has always kept front and center what could possibly feasibly be applied to newborn screening programs across the United States. So six millimeter punch is generous. Mark, I am impressed if you are getting good results with a single three millimeter punch.

**Mark Schleiss:**

We use all three (i.e., three 3mm punches).

**Sheila Dollard:**

That's good. We're ballpark. Anyway, so in this California study, the results were that the CMV birth prevalence was 0.5 to 0.8% depending on the group—the ethnic group and age and poverty level factor, known risk factors for congenital CMV. It was encouraging. If you compare that to papers that have done universal screening using culture of urine, which is the gold standard, then the birth prevalence is about .5 to 1.2%. So we know our sensitivity is not absolute. We never expected it to be absolute. So how sensitive it is, we don't know. We don't have any urine or saliva or whole blood to compare this to. But we think it's encouraging. Mark brought up several times the really key point here is, is viral load associated with sequelae? We're missing kids with the bottom 20% viral load. Is it possible that those are the kids that would be most likely to be okay anyway? That it's okay if a screening test misses the lowest or low infection? The methodology—if we're all going to talk and compare notes and compare progress it is really important to standardize our methodologies. And cost per test—I work with Scott Grosse and Danielle. We talk about economics a lot. Currently nucleic acid extraction and PCR combined are much more expensive than any cost per test for any other newborn screening. That's going to be a barrier we're going to have to deal with. And Mark, one comment I have about your question about cross-contamination between dried blood spots; Joanne Mei here at the CDC runs the quality assurance program for the newborn screening program. They have looked at that thoroughly and extensively. The good news is they have never had any evidence for any cross-contamination even with dried blood spots touching each other. So I think we don't have to do our own validations on that. So that's good news.

**Mark Schleiss:**

That's reassuring. Thank you.

**Sheila Dollard:**

But those are the main things I had to add to what Mark has done. That's about it.

**Danielle Ross:**

Thank as lot. That was great. Okay. So let's open this up for questions for another five minutes then we'll give Jeff the floor. Any questions for either Sheila or Mark or both?

**Scott Grosse:**

This is Scott Gross. This is a comment in terms of the cost. The cost for newborn screening using dried blood spots is typically less than \$1 to \$5 per disorder. It's well out of the ballpark. The frequency of the disorder generally quite rare, one in ten thousand. One in 20,000 or less common. It's also important to keep in mind the cost of EHDI doing universal newborn hearing screenings. The hospital is typically \$30 or more per infant screen. Hearing screening is considerably more common than any of the disorders that are being detected through dried blood spots. I think the most relevant comparison is how cost effective will this be for detecting additional cases of hearing loss since we expect probably at least half of the cases of hearing loss associated with congenital CMV will not be detected through newborn hearing screening. That's all.

**Mark Schleiss:**

Thank you. That's I think a key point. I think that's a subtle point that may be missed by individuals who sort of think of congenital CMV as all the damage that a baby is going to have is present at birth. That of course is not true, at least with respect to labyrinthitis and hearing loss. It is clearly a progressive lesion. I'll just throw out one comment. Sheila, I would be curious to know what you think of this question, too. One question I sort of toss around my lab all the time is what's the denominator? This is something we think about a lot. In other words, when we report a result and we have 10,000 genome copies in the dried blood spot DNA you extracted, is that 10,000 genomes per unit volume of blood? 10,000 genomes normalized against the amount of nucleic acid you extracted from that sample? In some laboratories where you have large volumes of blood to work with, people normalize the amount of viral DNA to the total number of leukocytes in the blood which is probably where the viral DNA resides. Of course we don't have the luxury of doing that with a newborn blood spot. Do we normalize the amount of viral DNA against a performed PCR with some housekeeping gene? Or do we make our best estimate and extrapolation knowing that a six millimeter punch is three microliters of blood or something like that. Then calculating it against that. I think this is another challenge. Every paper from every group around the world seems to have a different idea of what the denominator should be.

**Sheila Dollard:**

We take a very tiny amount of the DNA and we do a white blood cell count with PCR. Do a housekeeping RNA gene which gives us a white blood cell count. So we report the CMV viral load per million white blood cells. We haven't always done that. What we can also do is a -- as you were saying, Mark, we know a six millimeter punch is about 12 micro liters of whole blood.

We can report CMV copy number per milliliter of whole blood. Those are the two ways in which we report CMV viral load.

**Mark Schleiss:**

Thank you.

**Roger Eaton:**

This is Roger Eaton up in Boston. I would like to point out we talked about the cost of this, I think, [kind of foe cushion] in on the threshold being changed from no primary DNA analysis to a new disorder that has to kind of take up the whole burden of cost. It's just worth pointing out there are other conditions that on the horizon that people are working on that are going to require primary DNA analysis. So labs are going to start over the next few years, I'm sure, making DNA extractions on all the blood spots. When that threshold is overcome, then that same extraction should be usable for other tests or multiple tests. So it may not be, not saying the whole burden of the cost of the extraction piece may not be attributed only to CMV over the next couple of years.

**Sheila Dollard:**

Could I ask, the DNA extraction (this is Sheila Dollard at the CDC) is that for genetic tests or infectious agents?

**Roger Eaton:**

That's a good question. I think what Nancy Greene was mentioning on May Baker's work is also looking for low count. They are going to have to be of sufficient quality to be sensitive to low numbers of copies of DNA. It isn't looking for DNA in the same way. It's looking for existing circles. The prep should be similar.

**Caller:**

For genetic disorders there's thousands of targets there is but for a low copy number of viral infection there's not much there, very little. We've, in our work people will say, well, let us add this -- these three other PCRs to the DNA you're extracting. My answer is sorry, we use all of it. I understand your point. I'm saying for SCID people are going to be looking for diminishing amounts of these circles that indicate T cell function and when you are looking for diminishing amounts that go to zero, one is going to need to be sensitive. You're right that multiple tests that need to be sensitive may need to have more of that spot. I'm just pointing out the quality of the extraction which doesn't need to be as good for a mutation in all of the cells is probably going to be something that the screening programs will be working on anyway.

**Danielle Ross:**

Are there anymore questions? Okay. Jeff, if you would like to take the floor. Jeff instigated this whole thing. So go ahead and talk about monitoring protocols.

**Jeff Hoffman:**

I'm Jeff Hoffman. I manage Nebraska's early hearing and detection program. I guess it was about a month ago Danielle and I were having a routine conversation that kind of served as the catalyst for this call. And several years ago in Nebraska, the advisory committees of both the

newborn screening program and the EHDI program began to consider the feasibility of utilizing the dried blood spot for genetic and environmental causes of hearing loss. Of course as part of that, Nebraska has a ten point criteria for determining which disorders will be added or deleted from the newborn screening panel. We have looked at that based on the current technology and clinic knowledge. Also, we have developed seven possible options to move toward implementation. Of course this is over a period of years. As was mentioned earlier cost is one of those factors, as well as some of the ethical concerns that Mark mentioned. What would monitoring protocols for either later onset or progressive hearing loss look like if asymptomatic congenital CMV were identified? Not only what would the monitoring protocols look like, what would a state-wide EHDI system look like? Basically the purpose is to begin to stimulate some discussion about the monitoring piece and, as an EHDI program manager, starting to prepare for what may be facing us in a few years as the field develops. So basically I'm inviting you to begin consideration and discussion of those protocols and systems down the road. I'm not sure who all is on the call, a few basics on congenital CMV. Dr. Fowler at University of Alabama in Birmingham had indicated that the worldwide incidence is less than 1% of birth and, as Mark mentioned in Minnesota and other places, it's running about .5%. Of those that are born with CMV about 10% of symptomatic and about 90% are asymptomatic in that there are no indications that the baby has a positive stat for us that infection. For those that do have congenital CMV infection, there are several sequelae that are possible. Sensorineural hearing loss and mental retardation run at about 19%. There are also cerebral palsy and other neurologic problems. For those that are symptomatic, hearing loss runs about 30 to 40% but for those that are asymptomatic it's running about 5 to 10% according to recent article in the ASHA leader. There's a group of babies we don't know they are positive for CMV and will later develop hearing loss.

In 2006, Morton and Nance published an article in the New England Journal of Medicine that presented some causes of hearing loss. This is based on the United Kingdom. They reported that in their statistics that 1.86 of every thousand babies have a hearing loss. By four years of age that had increased to 2.7 per thousand 4-year-olds. They also apportioned out the percentage of those that were as a result of CMV. In extrapolating those out it would be about .39 of every thousand babies would have hearing loss due to congenital CMV. That would increase to .68 for every thousand by the age of four.

In departing from just the very basic background information on congenital CMV and beginning to look at the monitoring, the 2007 Position Statement of the Joint Committee on Infant Hearing departed from its recommendation in 2000 that babies with risk factors be monitored every six months. In the 2007 statement they now recommend that babies with risk factors have an audiologic evaluation at 24 to 30 months and the timing and number of hearing evaluations be individualized based on the likelihood of delayed onset hearing loss. Babies with congenital CMV and other disorders associated with that later onset should be monitored early and with more frequent assessments. The JCIH 2007 position statement did not define the early and more frequent statements. On the website they did post a clarification on February 13th of this year that interprets early and more frequent assessment at every six months or more depending on the clinical findings or concerns. It does begin to specify it more but there's still some variability there based on the clinical findings. As part of this I've tried to figure out what might be some recommended monitoring strategies for later onset hearing loss if there is a congenital

asymptomatic CMV. Back in 2001, there was a doctoral report done by Lisa Guillory in which she developed some guidelines for monitoring. Basically she divided her guidelines into two sets, one that had to do with monitoring for hearing loss and one that dealt with the vestibular sequelae. I'm going to address the audiologic piece here. She recommended that the audiologic assessment be conducted every three months for babies that were positive for CMV but had passed the newborn hearing screening. And she also suggested that perhaps screening with OAE and therefore avoiding the need for sedation at later ages would reduce the cost. She also suggested that, as soon as the child was developmentally able to participate in visual reinforcement VRA, a base line audiogram to be obtained with insert ear phones. Basically to get to that ear specific information so that unilateral hearing loss could be ruled out. The third guideline began to address the challenge of otitis media and transient conductive hearing loss that results. She suggested that for those babies who did have a middle ear dysfunction, bone conduction thresholds should be obtained as part of that. The fourth guideline looked at the intervention should be implemented as soon as possible if hearing loss is identified. Also, to accommodate the possibility of fluctuating or progressive sensorineural hearing loss, she recommended programmable hearing aids that could be adjusted as hearing sensitivity changed. Also to inform the parents of appropriate ways to monitor the child's hearing sensitivity without causing undue alarm or anxiety in the parents. This was simply one set of suggestions for monitoring. I guess as I look at it in terms of that suggestion, I wasn't finding any other work advocating on a more systematic statewide basis, but some of the questions that came to mind were, you know, looking at the recommendation that assessments occur every three months. Is that too frequent? As Mark mentioned what are the costs, the overall costs of having something that frequent? If that is too frequent, what should the frequency be? JCIH recommended six months or as recommended by the condition. We know that with the later onset hearing loss with asymptomatic congenital CMV occurs at various points, at various ages. How long should any monitoring system be and should that frequency of those evaluations change as the child grows older? What happens? Is there a point we say, no, the monitoring should cease that hearing loss is probably not going to be there. A question in my mind was she had recommended a possibility of an OAE screening. Is that sufficient or should there be some more extensive with regards to an audiologic assessment in addition early on such as an ABR? There was no mention of tympanometry as part of that workup for middle ear dysfunction and the transient conductive hearing loss. From a statewide EHDI perspective, one of the big question seems basically who has the responsibility for ensuring that the recommended monitoring occurs? The primary care provider, audiologist, EHDI program? Ultimately the parent? And of course part of that also is where is the responsibility, I think, as Mark alluded to, for the cost of all of this. And one thing that I was not finding that I think needs to be addressed as part of this there is also other sequelae in addition to later onset hearing loss, for example retinitis, what should the screening or monitoring of protocol look like for that. That concludes my piece of this. Definitely there are questions for consideration. I think that to my sense is kind of an ongoing dialogue perhaps in the EHDI community. I'm going to open it up for questions or comments at this time.

**Scott Grosse:**

The field is rapidly evolving. There's been some more recent publications on the sequelae. Sheila and Danielle and I published some articles. The frequency of the sequelae is somewhat lower than what Karen had reported previously. Also Morton and Nance what overstated the

proportion of hearing loss that is due to congenital CMV by focusing on the more severe level. If you look at just at children who have profound hearing loss, the proportion that is due to congenital CMV is substantially higher than children with a full spectrum hearing loss.

**Jeff Hoffman:**

Great, thank you.

**Caller:**

I think one challenge in comparing different reports around the world different countries may define a significant degree of hearing loss differently. In Great Britain if you have a 20 or 25-decibel threshold in one ear, perhaps, that may not qualify for special services or may not be defined as a disability as it might be in the United States. So I think there is certainly a lot of play in these numbers.

**Danielle Ross:**

I think that's a really good point. What definition you use in terms of hearing loss. Which frequencies are included in the pure tone average will all affect how people will project cost, the need, et cetera, et cetera. That's also something that of course we all know is not standardized from state to state or clinic to clinic but I think that also needs to be taken into consideration. Are there any people from other EHDI state programs who are considering what has been discussed who would like to give us a summary of what they are doing or what they are considering for the future? That was one of Jeff's questions—what are other states doing?

**Caller:**

This is Sheila from Washington state. We are currently doing a research project with the children's hospital where there are known patients who have hearing loss due to CMV and then they are using similar controls to see if they could have detected it in the newborn blood spots. So, in Washington we save our blood spots for 21 years so we have -- resources to go back and look at the integrity of the DNA and I'm not sure what specific markers they are doing. But from what I understand they are picking up the virus. So that's where we are at. It's going to be going on for another couple of years, research projects and we'll see if it ever becomes clinical.

**Mark Schleiss:**

Thank you. Are you able to say who the PI is on the project at children's hospital?

**Caller:**

Yes, Stephanie Messano. Actually it's Fred Hutchinson but they are working in collaboration with the Children's Hospital. And Susan Norton; it's been going on for about a year.

**Danielle Ross:**

I have a question for the states who do store the blood spots; how is that paid for? I'm sure it varies from state to state but if you keep them for 21 years that's quite a while. Isn't it relatively expensive to keep them?

**Caller:**

In Washington we keep ten years onsite in our newborn screening laboratory storeroom and then the other 11 years we archive in our office. I'm sure there's a storage charge. I don't know what it is. But I don't think it's that high. We just store them at room temperature. There aren't any special conditions.

**Danielle Ross:**

How about in Minnesota, do you have any idea how much that costs?

**Mark Schleiss:**

How much it costs? I don't. I mean you know it's, the spots are stored on state property in a warehouse in St. Paul and there are people that are on the state payroll as part of the newborn hearing or as part of the newborn screening program who are responsible for those. So I think the costs are probably related to paying rent on the building and transporting the material over there. I think the big challenge here in Minnesota, again, is this very vocal and politically active minority of parents around the state that are lobbying the legislature to say, you know, we need to destroy these blood spots after a couple of years as sort of a civil liberty issue. I don't think it's going to have a strong foothold here. I know in some states it has happened and I think this is a big challenge in the field in general.

**Caller:**

South Carolina several years ago they had a political fuss about storage of blood spots and as a result they passed new legislation which specified that parents could choose to have their children's specimens withdrawn -- as a result, very, very few parents actually chose to have it withdrawn. Now they have legislative authority. So it's better than what they had before when it was ambiguous.

**Mark Schleiss:**

That's a nice model. There is talk of legislature in Minnesota that would change all newborn screening in general from an opt out to an opt in kind of model and that of course would be catastrophic but there is a group that's very vocal on this issue here.

**Caller:**

Other states have other models. California stores the specimens for 21 years or indefinitely in a commercial freezer offsite. But minus 20 degrees centigrade.

**Mark Schleiss:**

Of course in Minnesota that's the ambient temperature half the year anyway.

**Danielle Ross:**

Were there any more questions for any of our speakers? We have the line until 11:30 but the call will probably end at 11:00.

**Ellen Amore:**

This is Ellen from Rhode Island. I'm just going to sort of throw out a thought for discussion if anyone wants to comment on it. I am thinking back to when universal newborn hearing screening was being developed and many states had a lot of arguments towards just screening

infants that have risk factors for newborn hearing loss. And then Scott made a very good point -- there's a higher frequency of hearing loss than many other conditions. It was too common if you only screen for risk factors you missed a lot of kids. If we apply that to the CMV screening are we going to -- if we focus a lot of effort on following up those kids, are we going to miss kids who have late onset hearing loss for other reasons? Should we be focusing more on early periodic screening for all? Should we add this as one more risk factor that we're already collecting? I know I'm pretty sure JCIH sort of backed off on the risk factor follow-up because for a lot of states it wasn't feasible. Does anyone have any thoughts on that?

**Al Mehl:**

That is Al Mehl in Colorado. Just one thought I wanted to add. I think one of the dilemmas is feasible to test a newborn baby that falls asleep a lot. The dilemma comes at six months, one year old, two years old. Not only do we have a good place to capture but the feasibility of getting a test is really difficult to maybe four years when a behavioral test is reliable. I think that's one of the dilemmas where we might have to look at risk factors in that age group only because a universal screening program would be so difficult.

**Caller:**

This is Vickie Thompson. I'm going to have to agree with Al. We're really struggling in Colorado right now with our part C system and Child Find system which is so overloaded they can't find audiologist to provide even evaluations for children who we know are at high risk. And so, yeah, I think if we can look at OAE screens or simple ways to maybe monitor these kids, I love the idea of screening every year but I'm challenged by all of it.

**Scott Grosse:**

I would like to make a plug to congenital CMV conference in November. On the last day, November 8<sup>th</sup>, there will be a session devoted to the issues involving newborn screening for congenital CMV. Also the call for abstracts is open for another two or three weeks. Anyone who is interested please submit an abstract.

**Caller:**

I'd like to sort of throw out a question maybe for Ellen to comment on in Rhode Island but anyone else on the call that might be in the northeast. For many years now I think it's Massachusetts and Connecticut have screened for congenital toxoplasmosis. My sense the yield on that and value and benefit of the program is unclear. I don't know if there have been similar discussions in Rhode Island or not, Ellen, or if you have any insights into the legislative process that led to that being added to the newborn screening panel in those states. I think it could be a very instructive situation to think about.

**Ellen Amore:**

Yeah, I am not familiar. Roger, are you still on the call? Roger Eaton runs the New England newborn screening program out of Mass. He's more familiar. I don't know the answer to that. I only know in Rhode Island we have a similar process to what Jeff Hoffman described there which is we have the criteria and we have to meet the criteria. We looked at the toxoplasmosis for Rhode Island since it is available through our regional lab. It hasn't met all the criteria. We also looked at CMV and sort of came to the same conclusion that neither one of those meet our

criteria yet. But obviously we're following the literature and the research to see how things develop.

**Caller:**

What about screening for CMV pre-natally? Most moms right now screened for toxoplasmosis. Anybody thought about obstetrics adding that to the panel prenatally?

**Caller:**

This will be a topic at the CMV conference in November. It's done in some European populations. Not in this country at all. There's some serious reasons why not. There's a lack of evidence of treatment.

**Caller:**

Then there's also the question if a mother tests positive then what do you do? Starts getting into the question of terminating pregnancies. Those sorts of things that are very difficult issues.

**Caller:**

I'd like to get back to the congenital toxoplasmosis issue. When Massachusetts started screening, there was some personal and professional interest in that. They never did much of an evaluation. When they had an advisory committee in '98 they only considered whether new disorders would meet the criteria. They did not evaluate whether the disorders they were already screening for would meet the same criteria. Denmark was screening for congenital toxoplasmosis and last year eliminated the test because they concluded it did not meet the criteria.

**Caller:**

That's very interesting. Has that Denmark experience been published?

**Caller:**

I'm not sure.

**Roger Eaton:**

This is Roger in Massachusetts. I think the Denmark decision was influenced by a large European study that looked at large data analysis that looked at primarily prenatal screening in a few newborn screening and they concluded that it wasn't -- they couldn't demonstrate significant advantages to the newborn screening.

**Caller:**

It is a complicated subject to address and I think it -- they did start it and then they pulled it back. Scott is correct that when it was started here in Massachusetts in '86 it didn't have the same scrutiny as new disorder being added in -- after 2000 would. And so I guess that's all I should probably say about that. Thank you.

**Caller:**

Of course, that's a serologic based screening.

**Caller:**

It may not be a reliable sensitivity for toxoplasmosis. I think for CMV it's much more likely to be sensitive.

**Caller:**

Are you looking for IGA antibodies and how much of the blood spot do you have to dedicate to the toxo analysis?

**Caller:**

It's a quarter inch spot so it's larger than the regular one. It's a combination of G and M. We're not in the standard protocol we're not very impressed with the IGA as being that helpful.

**Caller:**

Thank you.

**Danielle Ross:**

Any more questions or comments? Okay. If you have any questions for follow-up or anything please feel free to e-mail me. My e-mail address is [AYU0@CDC.gov](mailto:AYU0@CDC.gov) and my name is Danielle Ross. I think this has been quite a comprehensive call all the way from laboratory methods from considering what to do for follow-up and monitoring. Hopefully we'll be able to have a follow-up call at some point. I will let you know if that happens. We would like to thank our speakers again and thank you very much to everyone who called in and contributed to the discussion.

**Mark Schleiss:**

Thank you for organizing this Danielle and thank you, Jeff, for inspiring it. I think it would be terrific to see maybe a working group evolve from this.

**Caller:**

I agree. That would be very interesting and maybe have more regular calls.

**Caller:**

I think that's a good idea, too.

**Caller:**

Okay. Thank as lot. Bye.